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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/540,343	10/06/95	HALLMAN	D-20194

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EXAMINER	
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ART UNIT	PAPER NUMBER
1814	7

DATE MAILED: 11/25/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☒ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-26 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-26 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 06

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

* U.S. GPO: 1996-410-238/40050

Claims 1-27 are currently pending in U.S. Patent Application Number 08/540,343. Claims 29-32 have been cancelled as requested in the response filed 9-6-96 (paper #5).

The following is a quotation of 37 CFR 1.71(a)-(c):

(a) The specification must include a written description of the invention or discovery and of the manner and process of making and using the same, and is required to be in such full, clear, concise, and exact terms as to enable any person skilled in the art or science to which the invention or discovery appertains, or with which it is most nearly connected, to make and use the same.

(b) The specification must set forth the precise invention for which a patent is solicited, in such manner as to distinguish it from other inventions and from what is old. It must describe completely a specific embodiment of the process, machine, manufacture, composition of matter or improvement invented, and must explain the mode of operation or principle whenever applicable. The best mode contemplated by the inventor of carrying out his invention must be set forth.

(c) In the case of an improvement, the specification must particularly point out the part or parts of the process, machine, manufacture, or composition of matter to which the improvement relates, and the description should be confined to the specific improvement and to such parts as necessarily cooperate with it or as may be necessary to a complete understanding or description of it.

The specification is objected to under 37 CFR 1.71 because **the specification does not provide sufficient guidance to the skilled artisan regarding how to use the claimed invention.**

The specification is directed to the treatment of tumors through the administration of viruses, for example, adenovirus or herpesvirus, combined with radiotherapy. The instant invention is disclosed as being a novel and nonobvious methods of inhibiting tumor progression in vivo.

The working examples disclosed in the specification are severely limited to the in vivo use of a strain of HSV(R3616) and a genetically engineered strain of HSV(R899-6) which contains an exogenous TNF-α coding sequence.

The viruses and vectors used in the specification are not generic structures. Given the high level of unpredictability in the art of tumor treatment as well as gene therapy, it is not clear that the results achieved with a herpesvirus or a herpes virus vector would be predictive of the results that the skilled artisan would achieve upon implementing the claimed invention with an adenovirus or adenoviral vector. This is emphasized especially in light of the tremendous differences in the genome of adenoviruses, retroviruses, herpesviruses.

The specification fails to provide proper dosages of the viruses or viral vectors that are to be used in the claimed invention. Moreover, the claims broadly encompass any and all methods of administering the virus or vector to a tumor mass;

however, the guidance presented in the specification is severely limited to the direct administration of the HSV virus and HSV vector. The specification does not provide sufficient guidance regarding how to administer the compositions in any and all manners and achieve the results disclosed upon practicing direct intratumoral administration of a herpesvirus and herpesvirus vector encoding a cytokine.

Moreover, regarding the fact that the claims containing genetically engineered vectors encompass any and all cytokines, it is not clear that the art recognizes such as predictive or generally correlatable to the use of all cytokines because it is not clear at this juncture whether or not all cytokines would achieve the same effect upon reaching a tumor mass. Take for example, the information presented by the Dorudi et al. reference (Br. J. Surg. 80:566-572, 1993) page 569, column 1, first paragraph:

> "Although cytokine gene transfer offers an attractive approach to cancer vaccination, its use must be based on a clear understanding of both the tumor type and the immune response that the patient is able to mount against it. **This may vary even between patients with the same tumor and obviously limits clinical adoption of this strategy. Finally, the choice of therapy should also be guided by the growth requirements of the tumor, as the local production of certain cytokines can lead to enhanced growth of some**

tumors through an autocrine mechanism. Thus the delivery of an inappropriate cytokine to tumor cells may actually promote aggressive cell growth. Work is under way to rationalize the use of cytokine gene transduction of tumor cells to produce optimal stimulation of tumor-infiltrating effector cells."

Therefore, even if it were possible at some time to achieve sufficient cytokine gene transfer to any and all tumors (as is broadly claimed), the outcome would clearly be unpredictable as is evidenced by those of skill in the art.

Further, it must be noted that the working examples exemplifying the results of using the HSV vector containing the TNF gene sequence do not unambiguously establish that the HSV genome itself (and not the therapeutic TNF gene) was again responsible for the decrease in tumor burden and not necessarily the TNF construct. In other words, it is not clear that the results obtained using the genetically engineered construct were solely derived from the fact that the TNF gene had been inserted in the vector. The examples described using the virus alone achieved similar results even though they were not genetically engineered to express a cytokine.

Furthermore, regarding the claims that are directed to the administration of a viral vector containing a therapeutic gene, at the time the invention was made it was not clear that transfer

of any exogenous therapeutic gene could be effectively accomplished without having to undertake undue experimentation. This point is clearly supported by the art which recognizes the infancy of gene therapy and the tremendous amount of experimentation still required in the art. Kindly see the Marshall et al. article which evidences the alleged high level of unpredictability in the art. Even assuming that an effective combination of promoter and coding sequences exists, it is not clear that enough tumor cells can be transfected to provide any therapeutic benefit. Several recent reviews indicate that efficient delivery and expression of foreign DNA has not yet been achieved by any method. Marshall states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (p. 1050, col. 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (p. 1054, col. 3). James Wilson, one skilled in the art, saying that " '{t}he actual vectors - how we're going to practice our trade - haven't been discovered yet" (p. 1055, col. 2). Culver et al. , reviewing gene therapy for cancer, conclude that the "primary factor hampering the widespread application of gene therapy to human disease is the lack of an efficient method for delivering genes *in situ*, and developing strategies to deliver genes to a sufficient number of tumor cells to induce complete tumor regression or restore genetic health remains a challenge"

(p. 178). Hodgson discusses the drawbacks of viral transduction and chemical transfection methods, and states that " {d}eveloping the techniques used in animal models, for therapeutic use in somatic cells, has not been straightforward" (pp. 459-460). Miller et al. also review the types of vectors available for *in vivo* gene therapy, and conclude that " for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (p. 198, col.1). Therefore even if the claimed method could inhibit the growth of tumor cells *in vivo*, it would require further experimentation to develop a suitable system for delivery of the gene construct.

Moreover, it is not clear that the rodent model used in the specification would be considered correlatable to the results that the skilled artisan would observe upon practicing the invention in any and all animals, including humans. To support this allegation, Applicants' are respectfully requested to review the enclosed "REPORT AND RECOMMENDATIONS OF THE PANEL TO ASSESS THE NIH INVESTMENT IN RESEARCH ON GENE THERAPY". This report provides 40 pages of information which finds that although gene therapy has potential to become a useful tool for therapeutic cancer treatment, it remains highly unpredictable. The reference also establishes the difficulty with obtaining an animal model

which would be predictive of the results that the skilled artisan would observe in humans following therapeutic gene transfer. The art is clearly having problems with finding a predictive and faithful andimal model, kindly see the information presented by LaFont et al. page 1442, paragraph bridging columns 1 and 2:

> "The tumoral concept is attractive because it might explain the clinical picture, proposes a target (smooth-muscle-cell proliferation), is supported by animal models, and paves the way to treatment strategy (genes to inhibit smooth-muscle cell proliferation). The main drawback is related to the discrepancy between striking successes in various animal models and the general failure in human beings."

Furthermore, the tumor mass that was observed in the rodent models was an artificially created tumor mass and it is not clear how the results obtained using such would be correlatable to the results that would be obtained upon providing a virus or gene therapy vector thereof, and radiotherapy. Neither applicant nor the art have shown a correlation between these mice with implanted tumor cells and the tumor burden of an animal with a spontaneous tumor. For example, how does the size of tumors in applicants mice at the time of treatment compare in size to a spontaneous tumor?

It is therefore concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of correlatable working examples, the nature of the invention, the state of the prior art with its recognized unpredictability, and the breadth of the claims, it would require undue experimentation for others skilled in the art to practice the invention.

Claims 1-27 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 6, 8, 9, 12, 23-25 and 27 are rejected under 35 U.S.C. § 102(b) as being anticipated by Fujiwara et al.(Cancer Research 54:2287-2291, 1994).

Fujiwara et al. disclose the adenoviral mediated transfection of human cancer cells *in vivo* prior to administration of the DNA damaging compound cisplatin.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-27 are rejected under 35 U.S.C. § 103 as being unpatentable over art Wills et al. (Human Gene Therapy 5:1079-1088, 1994) taken with Fujiwara et al. (Cancer Research 54:2287-2291, 1994) and Boviatsis (Human Gene Therapy 5:183-194, 1994).

Wills et al. in disclosing the development and characterization of recombinant adenoviruses encoding human p53 for gene therapy of cancer specifically provide clear motivation on page 1086, column 2, for the combination of wtp53 gene insertion and subsequent radiation exposure:

> "Due to the high prevalence of p53 mutations in human tumors, it is possible that tumors which have become refractory to chemotherapy and irradiation treatments may

> have become so due in part to the lack of wild-type p53. By resupplying functional p53 to these tumors, it is possible that they will now become susceptible to apoptosis normally associated with the DNA damage induced by radiation and chemotherapy."

Fujiwara et al. teach the induction of chemosensitivity in human cancer cells *in vivo* by adenoviral mediated gene transfer of p53 into said cancer cells. Fujiwara et al. also clearly disclose the concomitant use of a chemotherapeutic drug, cisplatin for example, such that cell death may be enhanced thus leading to a decrease in tumor burden. Take for example, the information presented in the abstract:

> "These results support the clinical application of a regimen combining gene replacement using replication-deficient wild-type *p53* adenovirus and DNA-damaging drugs for treatment of human cancer."

Fujiwara et al. clearly teaches that the art was aiming at decreasing tumor burden and enhancing cell death through combination therapies which utilized well known chemotherapeutic strategies as well as viral mediated enhancement of cell killing.

At the time the invention was made, the use of adenovirus, HSV and retrovirus was well known in the art of therapeutic gene transfer. Take for example the information presented by Boviatsis et al.. The Boviatsis et al. article states on page

186, column 2:

> "Because adenovirus infections have been usually carried out at higher moi, the experiment was repeated at a moi of 50 for adenovirus and HSV. In this case, there was no difference in the percentage of *lacZ*-positive cells after incubation with either the adenovirus or HSV vectors (approximately 20%). There was extensive cytotoxicity at this moi with either vector, which probably resulted in the detachment of several *lacZ*-positive cells, leading to an artifactually lower estimate of gene transfer efficiency. Nevertheless, these results indicate that both retrovirus and HSV vectors efficiently transfer the *lacz* gene into rat 9L gliosarcoma cells, whereas much greater numbers of adenovirus vector are necessary to achieve a similar gene transfer efficiency."

Furthermore, it must be noted that at the time of filing of the instant application (October 6, 1995) it was well known in the art that infection of any cell with an adenovirus (albeit the virus also or an adenoviral vector construct) caused a CTL attack against the infected cell because of the expression of early and late viral gene products. Therefore, it was readily apparent that adenovirus infection of a cell would cause some type of destruction of said cell because of the immune response mounted against the adenoviral gene products expressed subsequent to infection by said adenovirus.

No claim is allowed.

Any inquiry concerning this communication from the examiner should be directed to Andrew Milne, whose telephone number is (703) 308-4213. The examiner can normally be reached from 7:00 to 4:00 (Eastern Standard Time) Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached at (703) 308-3153. The fax number for art unit 1804 is (703) 308-0294.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Andrew Milne

11-12-96

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